Complete Summary

GUIDELINE TITLE

American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome.

BIBLIOGRAPHIC SOURCE(S)

Polycystic Ovary Syndrome Writing Committee. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. Endocr Pract 2005 Mar-Apr;11(2):125-34. [64 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Polycystic ovary syndrome (PCOS)
- Complications of polycystic ovary syndrome including:
  - Cardiovascular disease (CVD)
  - Metabolic diseases including type 2 diabetes mellitus (T2DM)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention

Risk Assessment
Screening
Treatment

CLINICAL SPECIALTY

Cardiology
Endocrinology
Family Practice
Internal Medicine
Obstetrics and Gynecology
Preventive Medicine

INTENDED USERS

Health Care Providers
Patients
Physicians

GUIDELINE OBJECTIVE(S)

- To inform health care professionals and the public about the need to identify women with polycystic ovary syndrome (PCOS) and, once this diagnosis has been established, to search for metabolic and cardiovascular risk factors that may be associated with polycystic ovary syndrome
- To review the available data from studies that attempt to analyze these risks and their clinical consequences

TARGET POPULATION

Women with polycystic ovary syndrome (PCOS) at risk for metabolic and cardiovascular consequences

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation of Possible Polycystic Ovary Syndrome

1. Patient history, including detailed inquiry about growth and development, menarche, and menstrual pattern.
2. Blood pressure measurement
3. Measurement of body mass index (BMI) and waist circumference
4. Defining extent of hirsutism, degree of acne or alopecia
5. Measurement of
    - Total and free testosterone levels or a free androgen index
    - Serum levels of luteinizing hormone and follicle-stimulating hormone
    - Serum sex hormone-binding globulin
    - Serum prolactin, dehydroepiandrosterone sulfate and 17alpha-hydroxyprogesterone
6. Lipid profile, including high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides
7. Plasma insulin

8. Blood glucose level after glucose challenge
9. Pelvic ultrasonography

Treatment/Management/Risk Assessment in Women with Polycystic Ovary Syndrome

1. Risk assessment
    - Diabetes screening by age 30
    - Screening for metabolic disorders including insulin resistance syndrome (IRS)
    - Imaging studies for detection of cardiovascular diseases
    - Oral glucose challenge
    - Measurement of insulin
    - Measurement of atherogenic markers including C-reactive protein (CRP), fibrinogen, and homocysteine
2. Lifestyle modification
    - Weight loss
    - Controlled eating patterns
    - Regular aerobic exercise
    - Avoidance of tobacco
3. Treatment of lipid abnormalities
    - Dietary management
    - Pharmacotherapy
        - Statins
        - Fibrates
        - Niacins
        - Ezetimibe
        - Combination therapy
4. Treatment of blood pressure abnormalities
5. Metformin
6. Nonandrogenic oral contraceptive agents
7. Antiandrogen agents such as spironolactone in combination with an oral contraceptive agent
8. Ancillary use of electrolysis and laser therapy
9. Thiazolidinediones

MAJOR OUTCOMES CONSIDERED

- Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in women with polycystic ovary syndrome
- Predictive value of diagnostic tests
- Mortality
- Risk for adverse cardiovascular events, including myocardial infarction
- Effectiveness of treatment for improving hyperandrogenism and ovulation, increasing fertility, and reducing hyperinsulinism

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Not stated

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not applicable

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Clinical Evaluation of Polycystic Ovary Syndrome (PCOS)

The history should include a detailed inquiry about growth and sexual development, menarche, and menstrual pattern, as well as information to exclude other potential causes of oligomenorrhea, hirsutism, acne, and infertility. Physical findings of acanthosis nigricans and a hyperpigmented area on the nape of the neck or other areas such as the axillae or groin are suggestive of insulin resistance. Measurements of blood pressure, body mass index (BMI), and waist circumference must be made. Defining the extent of hirsutism and the degree of acne or alopecia is also essential.

Laboratory Assessment of Possible PCOS

No consensus exists among endocrinologists about the battery of laboratory tests that must be ordered in the assessment of women for PCOS. The following are the most commonly ordered laboratory tests, which are meant both to confirm the clinical diagnosis of PCOS and to evaluate for glucose intolerance and cardiovascular risk. Studies should be performed early in the morning, with the patient in a fasting state, and, in women with regular menses, sometime between days 5 and 9 of the menstrual cycle.

1. Several determinations of total and free testosterone levels or a free androgen index performed by a competent laboratory will help assess the status of androgens.
2. Serum levels of luteinizing hormone and follicle-stimulating hormone can be determined. An increased ratio of luteinizing hormone to follicle-stimulating hormone >2 is found in 60 to 70% of women with PCOS and is more likely to occur in nonobese than in obese women.
3. Measurement of serum sex hormone-binding globulin may reveal decreased levels in patients with PCOS.
4. Measurements of serum prolactin, dehydroepiandrosterone sulfate, and 17alpha-hydroxyprogesterone will provide useful information.
5. A lipid profile can be obtained, including serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and triglycerides.
6. Plasma insulin may be measured; clinicians should remember that methodologic inconsistencies occur and that insulin levels are not necessary for the diagnosis of the insulin resistance syndrome (IRS).
7. The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommend screening for diabetes by age 30 years in all patients with PCOS, including obese and nonobese women. The risk for diabetes is further heightened by a family history of diabetes, a personal history of gestational diabetes, and obesity, sedentary behavior, and ethnicity. Determination of a blood glucose level after challenge

with a 75-gram load of glucose may be performed. The usefulness of measuring insulin levels at baseline and 2 hours after administration of glucose is under study. Under some circumstances, earlier testing before the age of 30 years may be indicated. Because type 2 diabetes mellitus (T2DM) evolves over time, women with PCOS who initially test negative for diabetes should be periodically reassessed throughout their lifetime.

8. Pelvic ultrasonography, although nonspecific, affords a pretreatment view of the ovaries. The effect of treatment of PCOS can be monitored, in part, by noting ovarian size, follicle number, endometrial lining, and possible development of benign ovarian dermoids or other neoplasms (incidence of approximately 5 to 10%). The finding of morphologic evidence of polycystic ovaries on pelvic ultrasonography in 23% of apparently normal women limits its specificity in the diagnosis of PCOS. Several other endocrine pathologic conditions may mimic the ovarian morphologic appearance in PCOS. Thus, a history of oligomenorrhea and evidence of ovarian hyperandrogenism are key elements in defining PCOS.

Summary and Synthesis of Data on Cardiovascular Risk

In summary, several lines of evidence strongly support the concept that women with PCOS are at high risk for cardiovascular and metabolic disease.

1. The prevalences of both T2DM, a myocardial infarction-equivalent state, and impaired glucose tolerance (IGT), a condition associated with increased cardiovascular risk, are substantially increased in patients with PCOS. Accordingly, AACE and ACE recommend screening for diabetes in all patients with PCOS by age 30 years.
2. Multiple recognized cardiovascular risk factors are present in excess in women with PCOS (often several simultaneously). The result is a higher-than-usual prevalence of the Adult Treatment Panel III- and AACE-defined metabolic insulin resistance syndrome (IRS) in patients with PCOS.
3. Imaging studies in women with PCOS have uniformly identified a higher prevalence of anatomic and functional abnormalities indicative of existing underlying cardiovascular disease or dysfunction in comparison with findings in age-matched control subjects.

These observations are remarkable for their abundance, uniformity, and consistency, and they predict an increased risk for adverse cardiovascular events in patients with PCOS. To date, however, no prospective longitudinal study has assessed cardiovascular outcomes specifically in women with PCOS. Nonetheless, it is notable that a prospective large-scale study of women with oligomenorrhea who underwent follow-up for 1-1/2 decades reported a 2-fold increased risk for fatal myocardial infarction in this population. Most likely, a large proportion of these women had PCOS. Hence, this study provides indirect confirmation of increased adverse cardiovascular outcomes in patients with PCOS.

Despite the absence of prospective longitudinal studies, retrospective epidemiologic studies have been performed to assess cardiovascular outcomes in PCOS. Unfortunately, these studies have been of variable quality, and they have differed from one another with respect to diagnostic criteria, anthropometric and phenotypic characteristics, duration of follow-up, therapeutic intervention with bilateral wedge resection of the ovaries, and other factors. Nonetheless, most of

these studies have confirmed an increased risk for adverse cardiovascular outcomes in patients with PCOS.

Collectively, the foregoing substantive evidence indicates that women with PCOS are at high risk for cardiovascular disease (CVD). Even in the absence of definitive outcome studies, the evidence supports a strong recommendation that women with PCOS should undergo comprehensive evaluation for recognized cardiovascular risk factors and receive appropriate treatment based on findings.

Treatment of PCOS

Well-defined published data indicate a high risk for development of T2DM and CVD in women with PCOS. In view of the lack of protective effect of female sex on CVD risk in patients with diabetes, the associated risks of CVD are magnified in women with diabetes who have PCOS. Clearly, this situation means that PCOS is a general health disorder of young women, with potential for reversal of some of the associated risk with early diagnosis and treatment. Lifestyle modification with weight loss and exercise, avoidance of tobacco, correction of lipid abnormalities, and use of metformin may be of value. Metformin therapy not only reduces hyperinsulinism and improves steroidogenic dysfunction but also is helpful in achieving better regularity of menses and fertility potential. Thiazolidinediones have also been shown to decrease androgen levels, improve ovulation, and reduce progression to overt T2DM in patients with PCOS and IGT.

In view of the potential for and actual presence of numerous cardiovascular and metabolic risk factors in most women with PCOS, the role of the clinical endocrinologist is essential in the following:

1. Early recognition of the syndrome.
2. Lifestyle modification, with emphasis on the need for controlled eating patterns and regular aerobic exercise. Encouragement should be offered by an empathic physician, who will monitor the patient carefully during the course of treatment.
3. Measurement of glucose (and possibly insulin levels). An oral glucose challenge may be considered, particularly in obese women with PCOS and those with a family history of T2DM.
4. Detection and treatment of lipid abnormalities, with dietary measures first and then use of appropriate medications, such as a statin, fibrate, niacin, or ezetimibe (or some combination of these agents), as necessary.
5. Careful attention to and treatment of blood pressure abnormalities.
6. Measurement of atherogenic markers (C-reactive protein [CRP], fibrinogen, and possibly homocysteine).
7. Consideration of metformin therapy as the initial intervention in most women with PCOS, particularly in those who are overweight or obese. Metformin improves many metabolic abnormalities in PCOS and may improve menstrual cyclicity and the potential for pregnancy. Of note, metformin has not been approved by the US Food and Drug Administration for use in PCOS, although abundant medical literature supports its efficacy.
8. The use of a nonandrogenic oral contraceptive agent and an antiandrogen such as spironolactone for the skin manifestations of PCOS. The presence of hair thinning requires the maximal dose of spironolactone in conjunction with

an oral contraceptive agent. Ancillary use of electrolysis and laser therapy may also be helpful.

9. The use of thiazolidinediones in patients with impaired glucose tolerance or frank diabetes. The use of these agents to improve hyperandrogenism and ovulation is considered only investigational at this time. Thiazolidinediones are category C drugs; their use is contraindicated during pregnancy.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Early case finding and intervention are expected to result in a reduction of serious associated medical consequences.
- Metformin improves many metabolic abnormalities in polycystic ovary syndrome (PCOS) and may improve menstrual cyclicity and the potential for pregnancy.

POTENTIAL HARMS

Not stated

CONTRAINDICATIONS

CONTRAINDICATIONS

Thiazolidinediones are category C drugs; their use is contraindicated during pregnancy.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Polycystic Ovary Syndrome Writing Committee. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. Endocr Pract 2005 Mar-Apr;11(2):125-34. [64 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Mar/Apr

GUIDELINE DEVELOPER(S)

American Association of Clinical Endocrinologists - Medical Specialty Society

SOURCE(S) OF FUNDING

American Association of Clinical Endocrinologists (AACE)

GUIDELINE COMMITTEE

Polycystic Ovary Syndrome Writing Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Rhoda H. Cobin, MD, FACE (Chairperson); Walter Futterweit, MD, FACP, FACE; John E. Nestler, MD, FACP, FACE; Gerald M. Reaven, MD; Paul S. Jellinger, MD, FACP, MACE; Yehuda Handelsman, MD, FACP, FACE; Geoffrey P. Redmond, MD, FACE; Samuel S. Thatcher, MD, PhD, FACOG, FACE

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists (AACE) Web site.

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 1000 Riverside Avenue, Suite 205, Jacksonville, FL 32204.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 1, 2005. The information was verified by the guideline developer on October 5, 2005.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx.

NGC, AHRQ, and its contractor ECRI make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers

or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 9/4/2006